Synthesis and Rearrangements of Ethoxycarbonyl-substituted But-3-enyl- and Cyclopropylmethyl-(pyridine)cobaloximes

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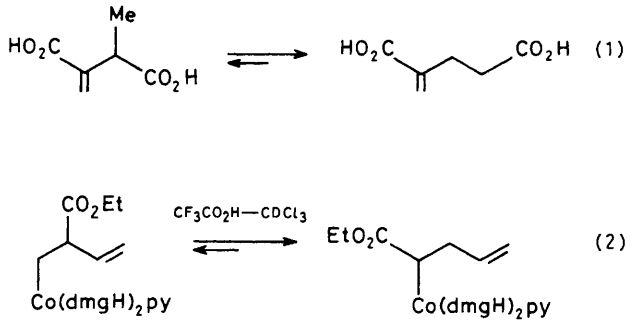
Isomeric ethoxycarbonyl-substituted but-3-enyl- and cyclopropylmethyl-(pyridine)cobaloximes undergo trifluoroacetic acid-catalysed equilibration; the significance of this and other observations for the mechanism of B_{12}-dependent α-methyleneglutarate mutase is discussed.

In continuation of our studies of the reactions of but-3-enyl- and cyclopropylmethyl-(pyridine)cobaloximes,[1] we have attempted to prepare these types of cobaloximes substituted with an ethoxycarbonyl group. Such compounds would be

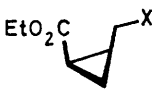


$CH_2{=}CHCH_2CH(X)CO_2Et$

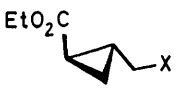
(1) a, X = Co(dmgH)$_2$py
b, X = Br
c, X = free radical

$CH_2{=}CHCH(CH_2X)CO_2Et$

(2) a, X = Co(dmgH)$_2$py
b, X = I



(3) a, X = Co(dmgH)$_2$py
b, X = I

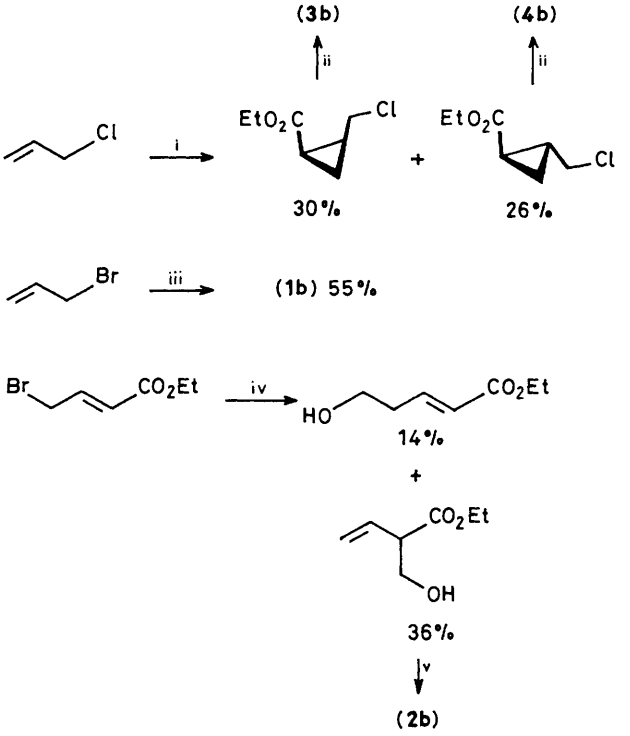


(4) a, X = Co(dmgH)$_2$py
b, X = I

$XO_2CHMeCH\overset{E}{=}CHCO_2Et$

(5) X = Co(dmgH)$_2$py

dmgH = monoanion of dimethylglyoxime
py = pyridine
All chiral compounds are racemic.



Scheme 1. *Reagents:* i, N_2CHCO_2Et added to an excess of allyl chloride containing $Rh_2(OAc)_4$;[3] products separated by spinning-band distillation; ii, NaI–acetone; iii, N_2CHCO_2Et added to an excess of allyl bromide in the presence of copper bronze catalyst;[4] iv, activated Zn, CH_2O–ether; v, Ph_3P, I_2–acetonitrile.[5]

better models for hypothetical intermediates in the adenosylcobalamin-dependent equilibration [*cf.* equation (1)] catalysed by α-methyleneglutarate mutase,[2] than the methyl-substituted systems previously described.[1] We have successfully prepared pure 1- and 2-ethoxycarbonyl-but-3-enyl(pyridine)cobaloxime [(**1a**) and (**2a**), respectively] and have observed their trifluoroacetic acid-catalysed equilibration [equation (2)]. Evidence will be presented for the formation of *cis*- and *trans*-(2-ethoxycarbonylcyclopropyl)methyl(pyridine)cobaloxime [(**3a**) and (**4a**), respectively] from *either cis*- or *trans*-1-ethoxycarbonyl-2-iodomethylcyclopropane [(**3b**) and (**4b**), respectively].

The alkylating agents (**1b**), (**2b**),† (**3b**),† and (**4b**)† were prepared as shown in Scheme 1.[3–5] Considerable experimentation was needed to obtain a satisfactory route to 3-ethoxycarbonyl-4-iodobut-1-ene (**2b**). Thus, alkylation of the anion of ethyl crotonate with either chlorodimethyl ether, formaldehyde (as paraformaldehyde), or di-iodomethane gave complex mixtures of products.[6]

For the preparation of cobaloximes from these alkylating agents the procedure employing bromo(pyridine)cobaloxime and $NaBH_4$ in ethanol was used.[7] From the bromide (**1b**) pure 1-ethoxycarbonylbut-3-enyl(pyridine)cobaloxime (**1a**)† was obtained reproducibly in 55% yield. With the iodide (**2b**) the best yield obtained for cobaloxime (**2a**)† was 25%. When the iodide (**3b**) reacted with (pyridine)cobaloxime(I) in ethanol the main product was the butenylcobaloxime (**1a**). Careful examination of the 400 MHz ^{1}H n.m.r. spectrum of the alkylcobaloxime fraction from column chromatography showed the presence in the sample of cobaloxime (**1a**) from the iodide (**3b**), and of both cyclopropylmethylcobaloximes (**3a**) and (**4a**), as evidenced by discrete resonances in the δ 0.5—1.5 region of the spectrum. When the cobaloxime (**1a**) was obtained from the iodide (**4b**) the main contaminant was the *trans*-cyclopropylmethylcobaloxime (**4a**) with a trace of the corresponding *cis*-isomer (**3a**). In one experiment almost pure (**4a**)† was obtained, whereas another gave mainly (**1a**). Usually, a *ca.* 1 : 1 mixture of (**1a**) and (**4a**) was obtained. These results can be explained by postulating an electron transfer mechanism[8] for the reaction of (pyridine)cobaloxime(I) with the iodides (**3b**) and (**4b**). Once (2-ethoxycarbonylcyclopropyl)methyl radicals are formed, these equilibrate *via* 1- and 2-ethoxycarbonylbut-3-enyl radicals. At equilibrium the dominant radical may be (**1c**), which is eventually captured by (pyridine)cobaloxime(II) to yield (**1a**). Alternatively (pyridine)cobaloxime(I) could react with the iodides (**3b**) and (**4b**) by an S_N2 mechanism giving cobaloximes (**3a**) and (**4a**), respectively. These could have undergone thermal equilibration with (**1a**) and (**2a**), and with each other *via* (**1a**) or (**2a**), during their

† New compounds gave ^{1}H n.m.r. and i.r. spectra, and combustion analyses [exact mass measurement of M^+ for (**3b**) and (**4b**)] in accord with their assigned structure.

preparation and/or subsequent manipulation (but see below). The factors which influence the relative proportions of (**1a**), (**3a**), and (**4a**) are under investigation.

When cobaloxime (**2a**) was treated with 1.0 M trifluoroacetic acid in deuteriochloroform at 20 °C, almost complete conversion into (**1a**) occurred over 3 days [*cf.* equation (2)]. Similar treatment of (**1a**) caused no apparent rearrangement (monitoring by ^{1}H n.m.r. spectroscopy), although partial degradation to 1-ethoxycarbonylbuta-1,3-diene occurred. These results stand in contrast to the much faster equilibrations of 1- and 2-methylbut-3-enyl(pyridine)cobaloxime, which gave the 2-methyl isomer as the predominant species at equilibrium.[1] The outcome of this reaction is determined by steric factors (primary alkyl cobaloximes are more stable than secondary ones). With the esters (**1a**) and (**2a**), the position of their equilibrium is evidently governed by the stabilising metal–carbonyl interaction in (**1a**) [$\sigma \rightarrow \pi$ hyperconjugation;[9] *cf.* ν_{max} (KBr) 1680s cm^{-1}] which is absent from (**2a**) [ν_{max} (KBr) 1728 cm^{-1}]. The conversion of (**2a**) into (**1a**) probably proceeds *via* (**3a**) or (**4a**), and indeed treatment of (**4a**) with 1.0 M trifluoroacetic acid in $CDCl_3$ for 6 h at 45 °C gave (**1a**). The reason that the rates of interconversions of (**1a**)—(**4a**) are slower than in the methyl-substituted series could be because an intermediate η^3-homoallyl species[1] is destabilised by replacing methyl by ethoxycarbonyl.

Conditions could not be found for the satisfactory thermal equilibration of (**1a**) and (**2a**) [no interconversion on heating either (**1a**) or (**2a**) at 50 °C for 20 h]. When either (**1a**) or (**2a**) was photolysed in deuteriochloroform without exclusion of air, the alkylperoxycobaloxime (**5**) was obtained.[10]

Our findings for the cobaloximes (**1a**)—(**4a**) suggest that alkylcobalamins postulated[11,12] as intermediates in the reaction catalysed by α-methyleneglutarate mutase [equation (1)] would be insufficiently reactive towards rearrangement. However, rapidly interconverting ethoxycarbonyl-substituted but-3-enyl and cyclopropylmethyl radicals are plausible intermediates in the formation of (**1a**) from (**3b**) or (**4b**). This supports a mechanism for α-methyleneglutarate mutase *via* intermediate carboxy-substituted but-3-enyl and cyclopropylmethyl radicals.[11,13]

We thank the E.E.C. for a scholarship to S. M.-K.

Received, 24th June 1983; Com. 839

References

1 M. P. Atkins, B. T. Golding, A. Bury, M. D. Johnson, and P. J. Sellars, *J. Am. Chem. Soc.*, 1980, **102**, 3630.
2 H-F. Kung and T. C. Stadtman, *J. Biol. Chem.*, 1971, **246**, 3378.
3 A. J. Hubert, A. F. Noels, A. J. Anciaux, and P. Teyssie, *Synthesis*, 1976, 600.
4 I. A. D'yakonov and N. B. Vinogradova, *J. Gen. Chem. USSR*, 1952, **22**, 1349.
5 G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Am. Chem. Soc.*, 1964, **86**, 964.
6 J. L. Herrmann, G. R. Kieczykowski, and R. H. Schlessinger, *Tetrahedron Lett.*, 1973, 2433.
7 M. R. Ashcroft, M. P. Atkins, B. T. Golding, M. D. Johnson, and P. J. Sellars, *J. Chem. Res. (S)*, 1982, 216.
8 M. Okabe and M. Tada, *Chem. Lett.*, 1980, 831.
9 K. L. Brown and E. Zahonyi-Budo, *J. Am. Chem. Soc.*, 1982, **104**, 4117.
10 N. W. Alcock, B. T. Golding, and S. Mwesigye-Kibende, manuscript in preparation.
11 B. T. Golding in 'B_{12},' ed. D. Dolphin, Wiley-Interscience, New York, 1982, Ch. 15.
12 P. Dowd, B. K. Trivedi, M. Shapiro, and L. K. Marwaha, *J. Am. Chem. Soc.*, 1976, **98**, 7875.
13 J. M. Pratt in ref. 11, Ch. 10.